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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/615,718	07/09/2003	Herman Waldmann	695458-79	9454

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EXAMINER

BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
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1643

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/615,718

Applicant(s)

WALDMANN ET AL.

Examiner

David J. Blanchard

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input checked="" type="checkbox"/> Other: <u>seq comply</u> . |

DETAILED ACTION

1. The preliminary amendments filed 02 January 2004 and 09 February 2004 have been entered in full.
2. Claims 1-16 are pending.

Election/Restrictions

3. Applicant's election of Group I, claims 1-15 in the reply filed 5/15/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
4. Claim 16 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.
5. Claims 1-15 will be examined on the merits.

Sequence Requirements

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. The specification contains sequences that are encompassed by the sequences rules and require sequence identifiers (SEQ ID numbers). For example, pg. 13, lines 14 (Gly₄Ser)₂, 22, 23 and pp. 15-16 (primers), pg. 16, lines 7 and 20.

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Applicants' cooperation is requested in reviewing the entire disclosure to ensure the present application is in sequence compliance.

7. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

8. APPLICANT IS GIVEN THE TIME ALLOTTED IN THIS OFFICE ACTION WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. §§ 1.821-1.825:

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Direct the response to the undersigned.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-15 are indefinite in the recitation "reduced side effects" in claim 1 as the exact meaning of the phrase is not clear. The phrase "reduced side effects" is not defined by the claims; the specification does not provide a standard for ascertaining the

direction, requisite degree or endpoint of the phrase "reduced side effects". Does the phrase mean that the therapeutic protein/antibody is modified to have reduced immunogenicity, reduced non-specific binding, reduced ability to bind Fc receptors, fix complement, reduced glycosylation, reduced cytokine release or some other reduced side effects resulting from cytokine release or is some other meaning contemplated by the phrase? As written, one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention.

b. Claims 1-15 are indefinite in the recitation that the therapeutic protein/antibody is modified with a compound that inhibits the binding of the protein to the therapeutic target and also produces a therapeutic effect by binding to the therapeutic target. It is not clear what is contemplated by the therapeutic protein/antibody that produces a therapeutic effect by binding to the therapeutic target, yet is modified such that binding to the therapeutic target is inhibited. Does the therapeutic protein/antibody bind the therapeutic target or not and what is the mode of action for producing a therapeutic effect if the therapeutic protein/antibody is modified with a compound that inhibits binding?

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (see MPEP 2163).

In the instant case, the claims are drawn to a pharmaceutical composition comprising a therapeutic protein or antibody being modified with a compound that is effective for reducing an side effects caused by the protein/antibody and wherein the therapeutic protein/antibody produces a therapeutic effect by binding to the therapeutic target. However, the written description in this case only sets forth one therapeutic protein, humanized anti-CD52 antibody (CAMPATH-1H), which is modified by linking to the CD52 mimotope QTSSPSAD and the CD52 mimotope mutant QTSAAVD and which reduces cytokine release (i.e., reduced side effect).

The specification on page 9 discloses that a compound may be a peptide or other molecule that is capable of binding to the antigen-binding site of the antibody and functions to inhibit binding of the antibody to the antigen. The specification on page 3 discloses that the term "therapeutic" encompasses both treating an existing disease condition or disorder and preventing and/or reducing the severity of a disease condition or disorder. The specification on page 11 discloses that examples of therapeutic proteins include hormones, enzymes, clotting factors, cytokines, chemokines and immunoglobulin-based fusion proteins and the term "antibody" includes all form of antibodies such as recombinant, humanized, chimeric antibodies and antigen-binding fragments thereof that are capable of binding a therapeutic target. Thus, the claims encompass an extremely large genus of therapeutic proteins and therapeutic antibodies linked to a genus of compounds including any peptide or molecule, and which is used for treating, preventing and/or reducing any disease condition or disorder. However, written description of the present application only reasonably conveys a therapeutic humanized anti-CD52 antibody, CAMPATH-1H, modified by linking two different peptides, CD52 mimotope (QTSSPSAD) or CD52 mimotope mutant 9 (QTSAAVD) in which the antibody-mimotope conjugate reduced the immune response (i.e., cytokine release) and had a therapeutic effect by binding CD52.

Thus, the instant disclosure does not provide sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or

disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus of therapeutic proteins and therapeutic antibodies linked to just any "compound" that inhibits the binding of the therapeutic protein or therapeutic antibody and has "reduced side effects" and produces a therapeutic effect. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. The description of humanized anti-CD52 antibody, CAMPATH-1H, modified by linking two different peptides, CD52 mimotope (QTSSPSAD) or CD52 mimotope mutant 9 (QTSAAVD) and having the claimed properties is not representative of the entire genus because the genus is highly variable, inclusive to a variety of sub-genera such as hormones, enzymes, clotting factors, cytokines, chemokines and immunoglobulin-based fusion proteins that are linked to any peptide or molecule (i.e., "compound"). Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Clearly, one of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the single disclosed CAMPATH-1H-mimotope species.

Further, it is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic

structural term) couched “in terms of its function of lessening inflammation of tissues” which, the court stated, “fails to distinguish any steroid from others having the same activity or function”. Similarly, the function of inhibiting binding of a therapeutic protein/antibody to the therapeutic target does not distinguish any “compound”, peptide or molecule from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Structural features that could distinguish the therapeutic protein-compound or therapeutic antibody-compound conjugates in the genus from others in the protein class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure does not describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the function of the binding of “therapeutic protein” or “therapeutic antibody” and the function of the “compound” alone are insufficient to describe the genus of therapeutic proteins and therapeutic antibodies and compounds linked thereto that “reduce side effects” and produce a therapeutic effect. One of skill in the art would

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reasonable conclude that the disclosure of a single humanized anti-CD52 antibody-mimotope conjugate, does not provide a representative number of species of therapeutic proteins and therapeutic antibodies linked or bound to a compound to describe the claimed genus.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the humanized anti-CD52 antibody, CAMPATH-1H, linked to the CD52 mimotopes, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

13. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising CAMPATH-1H (humanized anti-CD52 antibody), modified by linkage to a CD52 mimotope selected from QTSSPSAD and QTSAAVD, does not reasonably provide enablement for all other therapeutic proteins and therapeutic antibodies modified (i.e., bound or linked) with just any other peptide or molecule (i.e., compound), wherein the therapeutic protein or therapeutic antibody has reduced side effects and produces a therapeutic effect by binding to the therapeutic target. The specification does not

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enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The instant claims are broadly drawn to a pharmaceutical composition comprising a therapeutic protein or therapeutic antibody being modified with a compound that inhibits binding of the protein to the therapeutic target, wherein the modified therapeutic protein/antibody is effective for reducing side effects caused by the protein/antibody and produces a therapeutic effect by binding to the therapeutic target. Thus, the scope of the claims encompasses pharmaceutical compositions comprising just any therapeutic protein or just any therapeutic antibody that is bound or linked to just any compound, peptide or molecule that inhibits binding of the protein or antibody to the therapeutic target and the modified protein/antibody reduces side effects caused by the protein and produces a therapeutic effect by binding to the therapeutic target. The teachings and exemplary guidance in the specification are limited to a humanized anti-CD52 antibody (CAMPATH-1H) linked to a CD52 mimotope, which reduces binding to CD52, but is competitively displaced by CD52 in vivo due to more favorable association

and dissociation binding kinetics and the CAMPATH-1H-mimotope conjugate reduces cytokine release. There is no guidance or direction of any other therapeutic protein/antibody bound or linked to just any compound, molecule or peptide that inhibits binding of the protein or antibody to the therapeutic target, reduces side effects and produces a therapeutic effect by binding to the therapeutic target. Thus, the scope of the claims is extremely broad relative to the teachings and guidance provided in the disclosure. The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology, 111: 2129-2138, November 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology, 8(3):1247-1252, Mar 1988). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc. Natl. Acad. Sci. USA, 84:6408-6411, 1987. Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563

(1975). Further, Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose the dissociation of immunoreactivity from other activities when constructing analogs (see entire document). Thus, the state of the art recognized that it would be highly unpredictable that linkage of just any compound, peptide or molecule to a therapeutic protein or a therapeutic antibody specific for a therapeutic target or even the linkage of a particular compound, peptide or molecule with just any therapeutic protein or just any therapeutic antibody would provide the requisite association and have the appropriate affinity wherein upon administration of such modified therapeutic protein or antibody, the compound, peptide or molecule would inhibit by obstruction the binding site of the therapeutic protein or antibody, thereby "reducing side effects" and displacement of the compound, peptide or molecule from the binding site upon binding to the therapeutic target produces a therapeutic effect. One of skill in the art could not predictably extrapolate the teachings in the specification limited to a humanized anti-CD52 antibody linked to a CD52 mimotope to a therapeutic protein or therapeutic antibody bound or linked to a compound, peptide or molecule that inhibits binding of the protein or antibody to its therapeutic target and wherein the protein or antibody gradually accumulates on cell-bound or target antigen due to favorable association and dissociation constants relative to that of the compound, peptide or molecule, thereby "reducing side effects" and producing a therapeutic effect. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more

may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Burgess et al, Lazar et al, Schwartz et al, Lin et al, Lederman et al and Li et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed pharmaceutical compositions comprising a therapeutic protein or therapeutic antibody bound or linked to a compound, peptide or molecule that inhibits binding of the protein or antibody and produces a therapeutic effect by binding to the therapeutic target with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed compositions and absent working examples providing evidence which is reasonably predictive of the claimed compositions, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-3, 5-6 and 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hale G (Immunotechnology, 1:175-187, 1995).

Hale G teaches an anti-CD52 humanized antibody, CAMPATH-1, reversibly bound by the synthetic peptide, QTSSPSAD, a CD52 mimotope that inhibits binding of CAMPATH-1H to human lymphocytes expressing CD52 by about four fold and the antibody is disclosed in various buffers including PBS, which are reasonably interpreted to be a "pharmaceutically acceptable carrier" (see entire document, particularly pg. 176, col. 2, 2nd paragraph, pg. 179, col. 2), pg. 183, col. 2, 2nd paragraph and Fig. 8).

Products of identical chemical composition cannot have mutually exclusive properties.

A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

See MPEP 2112.01. Thus, the CAMPATH-1-CD52 mimotope bound complex taught by Hale necessarily reduces side effects and produces a therapeutic effect by binding to CD52 and the amount of antibody that binds to the target increases as the mimotope is displaced from the antigen-binding site of the antibody, all intrinsic properties of the CAMPATH-1-CD52 mimotope bound complex of Hale.

Thus, Hale anticipates the claims.

16. Claims 1-2, are rejected under 35 U.S.C. 102(b) as being anticipated by Waldmann et al (WO 97/31024, published 8/28/1997).

Waldmann et al teach a therapeutic antibody, Campath-1, that binds a therapeutic target (i.e., CD52) and is modified by mutation(s) in the CDRs to reduce affinity, which is interpreted to be modified with a compound that inhibits binding of the antibody and wherein the antibody induces immunological tolerance caused by Campath-1 (i.e., "reducing side effects") and the modified Campath-1 still has some binding affinity for the cell surface antigen, CD52 and thereby produces a therapeutic effect. Further, Waldmann et al teach the *in vivo* administration of the antibody and one skilled in the art would readily envisage that the modified Campath-1 antibody is present in a form suitable for administration, i.e., a pharmaceutical carrier is necessarily present (see entire document, particularly pp. 8-10 and examples).

Thus, Waldmann et al anticipate the claims.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6-10, 13-16 and 35 of copending Application No. 09/979,948.

The present claims are drawn to a pharmaceutical composition comprising a therapeutic protein that binds to a therapeutic target, said protein being modified with a compound that inhibits binding of the protein to the therapeutic target, said modified protein being effective for reducing side effects caused by the protein and for producing a therapeutic effect by binding to the therapeutic target and a pharmaceutical carrier, wherein the therapeutic protein is an antibody that includes an antibody combining site that binds to the therapeutic target and the compound is bound or linked to the antibody combining site of the antibody and the compound is a peptide. Further, the modified therapeutic antibody, wherein the avidity of the modified antibody is at least 4 fold less and no more than 100 fold than the unmodified antibody, wherein the antibody is aglycosylated and wherein the compound is reversibly bound to the antibody combining site, whereby the amount of antibody that binds to the target increases as the compound is displaced from the antibody combining site and the antibody is aglycosylated in the Fc portion and Fc binding is essentially eliminated and wherein the antibody is a non-human or chimeric antibody.

Claims 1, 6-10, 13-16 and 35 of copending Application No. 09/979,948 are drawn to a pharmaceutical composition comprising a therapeutic protein that binds to a therapeutic target, said protein being modified with a compound that inhibits binding of the protein to the therapeutic target, said modified protein being effective for reducing

side effects caused by the protein and for producing a therapeutic effect by binding to the therapeutic target and a pharmaceutical carrier, wherein the therapeutic protein is an antibody that includes an antibody combining site that binds to the therapeutic target and the compound is bound or linked to the antibody combining site of the antibody and the compound is a peptide . Further, the modified therapeutic antibody, wherein the avidity of the modified antibody is at least 4 fold less and no more than 100 fold than the unmodified antibody, wherein the antibody is aglycosylated and wherein the compound is reversibly bound to the antibody combining site, whereby the amount of antibody that binds to the target increases as the compound is displaced from the antibody combining site and the antibody is aglycosylated in the Fc portion and Fc binding is essentially eliminated and wherein the antibody is a non-human or chimeric antibody.

The only difference between the two sets of claims is that the instant claims also encompass a pharmaceutical carrier whereas claims 1, 6-10, 13-16 and 35 of copending Application No. 09/979,948 do not. However, adding a known component such as a pharmaceutical carrier to form a pharmaceutical composition for therapeutic use is within the purviews of one of ordinary skill in the art. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to add a pharmaceutical carrier to the claimed pharmaceutical compositions of copending Application No. 09/979,948 to facilitate the administration of the pharmaceutical composition in patients. Thus, because both set of the claims encompass a pharmaceutical composition comprising the same therapeutic protein/antibody with the

same modification and binding to the same therapeutic target, the claims are *prima facie* obvious over each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

19. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Gilliland et al., (J of Immunology, 162:3663-3671, 1999). Gilliland et al teach a therapeutic antibody, CAMPATH-1H (humanized rat anti-human T lymphocytes antibody, page 2-3), that is modified by mutation of amino acids in the CDR2 region of a heavy chain and modified antibody induces immunological tolerance to the wild type antibody.

James et al (J. Mol. Biol., 289:293-301, 1999). James et al teach structure of the therapeutic antibody, CAMPATH-1H Fab in complex with the peptide mimotope, TSSPSAD.

20. No claim is allowed.

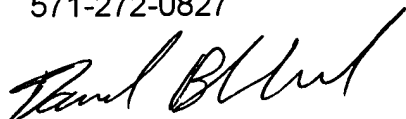
21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at

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(571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

A handwritten signature in black ink, appearing to read "David Blanchard", written in a cursive style.

Application No. 10/615,718

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING
NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other: _____

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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